TECHNICAL PAPER

ISSN 1047-3289 J. Air & Waste Manage. Assoc. 50:1514-1531
Copyright 2000 Air & Waste Management Association

Comparison of Ambient PM Risk with Risks Estimated from PM Components of Smoking and Occupational Exposures

John F. Gamble and Mark J. Nicolich

Occupational and Public Health Division, ExxonMobil Biomedical Sciences Inc., Annandale, New Jersey

ABSTRACT

Air pollution studies are based on individual-level health response data and group-level exposure data. Therefore, exposure misclassification occurs, and the results may be biased to an unknown magnitude and direction. Testing the validity of such associations requires a study design using individual-level data for both exposure and response. One can test the plausibility of group-level PM risk estimates by comparing them to individual-level estimates of risk from constituents of ambient air. The twofold purpose of this review is to consider the internal consistency of risks estimated from the three major PM cohort studies and to determine individual-level mortality risks associated with ambient concentrations of tobacco smoke and occupational exposures and compare them with risks associated with ambient PM.

The paper demonstrates the risks are not consistent within and between the PM cohort studies. Higher ambient concentration risks (ACRs) from the ambient PM cohort studies are not coherent with ACRs derived from individual-level smoking and occupational risks for total, cardiopulmonary, and lung cancer mortality. Individual-level studies suggest increased risk of mortality cannot be measured with reliability at concentrations found in ambient air.

INTRODUCTION

Air pollution studies are based on individual-level health response data and ecological or group-level exposure data. Therefore, exposure misclassification occurs, and the results may be biased to an unknown magnitude and direction. In epidemiology, a study using group-level data is generally a hypothesis-generating study and not suitable for testing a hypothesis. Tests to verify or refute such associations require as a minimum a study design using individual-level data for both exposure and response. One can test the plausibility of PM risk estimates from prospective cohort studies by using individual-level estimates of risk from constituents of ambient air.

The method used to test the PM/mortality hypothesis is to determine the individual-level mortality risks associated with ambient concentrations of tobacco smoke and occupational exposures and compare these risks (called ambient concentration risks or ACRs) with mortality risks associated with ambient PM which have no individual-level exposure data. This method is basically the same as the calculation of unit risk (*UR*) except we use ambient concentration as the unit of exposure. The individual-level measures of occupational exposures include carbon black, diesel exhaust, polyaromatic hydrocarbons (PAHs), transition metals, and SiO_2.

It would be most useful in an empirical test of coherence/consistency if the particulate was similar to ambient $PM_{2.5}$. Combustion PM is an important source of fine particulate, and a suggested cause of the associations in the cohort studies.[1] PAHs and trace metals are also part of the emissions from combustion, and trace metals have been proposed as a possible etiological agent. If the primary concern is size, then fine inorganic particulate in metal fumes and welding fumes may be important. Receptor modeling indicates fugitive dusts, including SiO_2, are also major sources of PM. Tobacco smoke is a major source of exposure to fine PM, as mainstream smoke for smokers and sidestream smoke for both smokers and nonsmokers. Environmental tobacco smoke (ETS) is also found in ambient air.

This paper will consider the hypothesis that current levels of ambient PM increase the risk of mortality. The basis for this hypothesis comes from three prospective

IMPLICATIONS

The lack of consistency within the PM cohort studies and the divergence of the PM cohort-based risks from smoking and occupational exposures to PM constituents cast doubt on the mortality-PM exposure hypothesis. The lack of coherence suggests that regulation of PM exposure below current standards will not reduce mortality, and by extension will divert money from beneficial projects to reductions in materials that do not affect mortality or morbidity.

RWLP0232

This article is for individual use only and may not be further reproduced or stored electronically without written permission from the copyright holder. Unauthorized reproduction may result in financial and other penalties (c) AIR & WASTE MANAGEMENT ASSOC

FROM ISI DOCUMENT SOLUTIONS (MON) 08. 13' 01 10:18/ST. 10:01/NO. 3560638488 P 4/21

PM3006519021

Source: https://www.industrydocuments.ucsf.edu/docs/nngj0001

cohort studies—the Six Cities cohort,[2] the American Cancer Society (ACS) cohort,[1] and the latest update of the Seventh Day Adventist cohort, called AHSMOG.[3,4] The major categories of mortality in these studies were total mortality from all causes, cardiorespiratory mortality, and lung cancer. Nonmalignant respiratory disease (NMRD) was also considered in the AHSMOG and mentioned in Six Cities. These studies also provided estimates of individual-level risk from smoking.

The purpose of this paper is to address questions regarding the risks of increased mortality associated with PM constituents of ambient air. The major focus will be on the smoking risks estimated from the air pollution studies and on occupational cohorts where there are quantitative exposure-response (E-R) trends based on individual-level estimates of exposure, similar to Oxman et al.[5] In this way, individual-level risks associated with high exposures to primarily single constituents of ambient air can be compared with group-level risks associated with ambient PM. The basis of the comparison will be the ACR. The ACR is the risk associated with average concentrations of constituents measured in ambient air.

Answering the following questions will test the coherence of the hypothesis that ambient air concentrations of approximately 20-μg/m³ PM significantly increase mortality.

- Is there an internal consistency of results in the PM cohort studies, both within and between the studies, sufficient to fulfill the causal criterion of consistency? If there is inconsistency, are there any results that do meet the coherence causal criterion?
- Is there external coherence between the results of PM cohort studies and results from smoking and occupational cohorts? Are the ACRs from individual-level studies similar to group-level risks? Can individual-level risks derived from smoking and occupational cohorts be reliably estimated at exposure levels found in ambient air?

A finding of similar ACRs supports the PM/mortality hypothesis, while a finding of dissimilar ACRs detracts from a causal association.

The Methods section explains the procedures for calculating risks and the units of exposure used for each air pollutant. Results are then presented for ACRs associated with ambient PM and tobacco smoke from the air pollution studies for total, cardiopulmonary, and lung cancer mortality and NMRD. Then the results from occupational cohorts are presented by the specific component found in ambient air. PM without a size qualifier refers to PM of several sizes that can be determined from the context. For example, PM is used for the three PM cohort studies where the size for Six Cities and ACS is $PM_{2.5}$ and for AHSMOG it is PM_{10}.

METHODS

A computer search of the literature from 1966 to the present was conducted for mortality studies of occupational cohorts exposed to carbon black, coal smoke, coal tar, diesel exhaust, PAHs, transition metals, or inorganic dust. Criteria for selection of studies included (1) individual-level exposure data, (2) minimal confounding, and (3) quantitative exposure-response analysis where it is possible to estimate risk per unit exposure.

The exposure metric is cumulative exposure, and is converted to an estimated lifetime intensity of exposure for 70 years; the units are μg/m³. The protocols for calculating ACRs relating to ambient PM, cigarette smoke, and occupational exposures are given as examples below.

Conceptually, the method is as follows. There are two types of studies reporting risks associated with PM. One type uses ambient PM concentration as the group-level estimate of lifetime exposure, which is in μg/m³. The second type uses exposure to PM at work or personal exposure to tobacco smoke as the individual-level estimate of cumulative exposure for a working lifetime or pack-years of exposure to tobacco smoke (in μg/m³ years). For these occupational/smoking studies, the exposures are converted to a lifetime intensity in units of μg/m³. Now lifetime exposure intensities to PM are in the same exposure units, that is, μg/m³. Using the reported risks and exposures from these studies, β coefficients were calculated. To make the comparison between the estimates from these two types of studies more understandable, a relative risk (RR) was calculated based on the coefficient and an ambient exposure; this risk is called the ACR. The ACRs from the two types of studies are then compared for consistency.

Sample Calculation of ACR

Development of the ACR. One of the bases of comparison used in this paper is the ACR. The ACR is based on an RR and ambient exposure concentration. Exposures in the PM cohort studies are reported in lifetime intensities and need no alteration. The occupational exposures are converted to lifetime exposures using standard conversion techniques assuming a 70-year lifetime and a 40-year working lifetime.[6] It is assumed that the RR is exponentially related to exposure, E, by the equation $RR = \exp(\beta \times E)$. The factor β is akin to the U.S. Environmental Protection Agency (EPA) UR factor. In the current paper, the β factor was estimated from the RR associated with a standard exposure relative to a zero exposure. This distinction is important mainly in occupational studies where the exposure in the base comparison group is often greater than zero. In these cases, the β factor is estimated from $RR = \exp(\beta \times (E - E_0))$, where E_0 is the base exposure. The base comparison group includes the lowest exposed or nonexposed referent group in case-control studies or other

FROM ISI DOCUMENT SOLUTIONS (MON) 08. 13' 01 10:19/ST. 10:01/NO. 3560638488 P 5/21

PM3006519022

Source: https://www.industrydocuments.ucsf.edu/docs/nngj0001

designs where the RR is 1.0, and in cohort studies where the SMR is for the entire cohort and the reference population SMR is set at 1.0, so in effect the SMR for the exposed group becomes an RR.

Comparisons of the β factors provide estimates of relative toxicity or change of risk with a unit change in exposure. However, the goal of the current analyses is to compare risks associated with an ambient exposure rather than with the same unit of exposure for each of the different PM constituents. A comparison based on a fixed exposure, such as 10 μg/m³ (or 1 μg/m³ as in UR), would provide a distorted view because, for example, while 10 μg/m³ is reasonable for PM it is too extreme for Cr, which occurs in small fractions of 1 μg/m³. To overcome these difficulties, the exposure unit chosen for comparison was the average concentration of the material in contemporary ambient air or contemporary ambient exposure concentration. The estimated ambient exposure concentrations used in these analyses are presented in Table 1 and represent the ambient concentration used to estimate the ACR for that particular constituent of ambient air. While there might be some differences of opinion as to what values to choose for contemporary ambient exposure concentration, the values are mainly for comparison purposes, and other ambient values could be substituted and new comparisons made.

Contemporary ambient exposure concentrations for PM in the air pollution studies are set at 20 μg/m³ since this is the approximate difference in $PM_{2.5}$ between high- and low-polluted cities in both the Six Cities and ACS studies. It also approximates the interquartile difference in PM_{10} in the AHSMOG cohort. The smoking and occupational cohorts are exposed to ambient air plus air that is enriched with excess PM from exposures at work (diesel exhaust, PAHs, SiO_2, and trace metals) or from personal habits (tobacco smoke). These extra exposures often are many times greater than the concentrations found in ambient air. The question of whether it is possible to estimate risk to substances found in the low concentrations of ambient air (relative to work/smoking exposures) can only be answered when the unit of exposure is that of ambient concentrations. All these substances at some concentration are associated with some increased risk for at least one cause of death. Even when the exposures are estimated for a 70-year lifetime instead of a 40-year working lifetime, the average smoking and occupational exposures generally exceed ambient concentrations in the air pollution studies (see Figure 1). ACRs estimated from the smoking/occupational cohorts provide a most favorable situation for estimating risk at concentrations found in urban air since the slope of the E-R curve is influenced by both the high occupational/smoking exposure and ambient PM. If the risks from these known toxins cannot be estimated with reliability, it is implausible that one could estimate increased risks from ambient PM alone.

The following examples outline the conversion process from the published RR to the estimated ACRs.

Smoker Example. Dockery et al.[3] indicated that a 25 pack-year smoker has an RR of 1.26 for total mortality. (A pack-year is 20 cigarettes/day for 1 year.) On average, men in the ACS cohort study smoked cigarettes containing 15-mg tar/cigarette and women smoked cigarettes containing 10-mg tar/cigarette. Assume 18 m³ of air breathed/day.[7]

- Male tobacco exposure for 1 day = 15-mg tar/cigarette × 20 cigarettes/day = 300 mg/day.
- Daily mean exposure while smoking = (300 mg/day)/(18 m³/day) = 16.7 mg/m³.
- Lifetime mean exposure = (16.7 mg/m³) × (25 years smoking/70 years lifetime) = 5.95 mg/m³ = 5950 μg/m³.
- Knowing from the Six Cities that for 25 pack-years the RR is 1.26 and the lifetime exposure is 5950 μg/m³, β is calculated as ln(1.26)/5950, or 3.9×10^{-5} (μg/m³)$^{-1}$.
- The male lifetime UR for 1-μg/m³ tobacco PM is exp (3.9×10^{-5}) = 1.00004. The ACR is 1.0000078 per 0.20 μg/m³ for ETS.
- The corresponding female lifetime UR for 1-μg/m³ tobacco PM is 1.00003. The ACR is 1.0000052 per 0.20 μg/m³ for ETS.

Occupational Example. The occupational studies have assessed the E-R using cumulative exposure, which is a lifetime exposure. Lifetime intensities were estimated by dividing lifetime exposure by 70 years. In cohort studies, results may be given as standardized mortality ratios (SMRs) associated with specific exposures. To develop ACRs, a "no exposure" group was arbitrarily set at 1.0 and

Table 1. Concentrations in ambient air of constituents used in calculating ACRs.

Material	Contemporary Ambient Exposure Concentrations (μg/m³)
PM	20
ETS	0.2
Diesel exhaust	1.0
Carbon black	0.3
PAHs	5.0
BaP	0.002
SiO_2	3.0
As	0.00095
Cr	0.00065
Ni	0.0038

FROM ISI DOCUMENT SOLUTIONS (MON) 08. 13' 01 10:20/ST. 10:01/NO. 3560638488 P 6/21

PM3006519023

Source: https://www.industrydocuments.ucsf.edu/docs/nngj0001

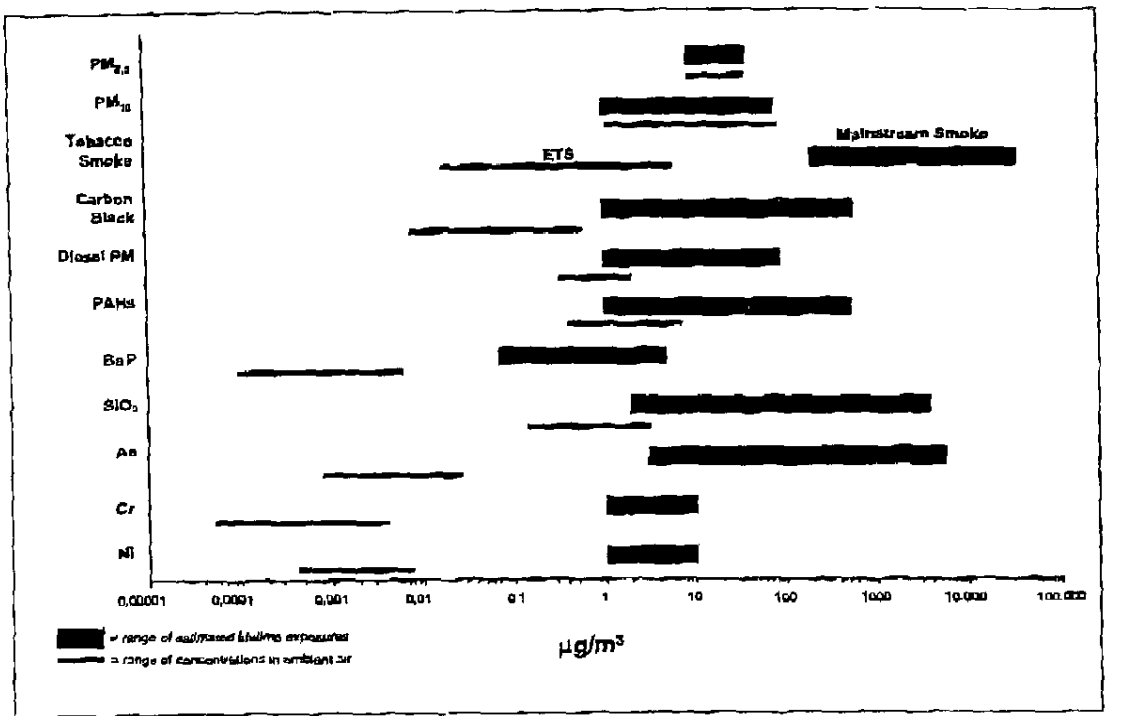

Figure 1. Concentrations of PM, tobacco smoke, and occupational agents in ambient air and estimated average exposures over a lifetime.

ACRs estimated accordingly. In several studies, an average exposure could be estimated from E-R analyses for a specific cause of death. If only SMRs are reported, ACRs are estimated using the overall SMR and average exposure from the E-R analysis.

Assume an RR of 0.67 is associated with an exposure of 1.9 mg/m³ years respirable SiO_2 in an occupational setting. The UR and ACR are calculated as follows.

- First, the occupational exposure is 1.9 mg/m³ years.
- Lifetime exposure is converted to lifetime intensity of exposure by (1900 µg/m³ years/70 years) = 27.1 µg/m³.
- Using the RR/exposure relation, β is calculated as $\ln(0.67)/27.1$, or -1.48×10^{-2} $(\mu g/m^3)^{-1}$. This yields a lifetime UR/µg/m³ of 0.9854. The lifetime ACR for SiO_2 is 3 times the UR, or 0.957 (3-µg/m³ SiO_2 in ambient air $X = 1.48 \times 10^{-2}$ $(\mu g/m^3)^{-1}$).
- Therefore, the lifetime UR is 0.9854 for 1-µg/m³ occupationally based respirable SiO_2 PM, and the lifetime ACR for SiO_2 is 0.957 for 3-µg/m³ respirable SiO_2 found in ambient air.

Air Pollution Example. The average ambient concentration used in the PM cohort studies is the lifetime intensity and needs no further calculation. For example, in the Six Cities study, an increase of 18.6-µg/m³ $PM_{2.5}$ is associated with an RR of 1.26 for total mortality. These values are based on a reported risk for Steubenville versus Portage, where the average lifetime exposure is 33.6 µg/m³ for residents of Steubenville, the most polluted city, and 11.0 µg/m³ for Portage, the least polluted city, a difference of 18.6 µg/m³.

- Lifetime mean exposure = 18.6 µg/m³.
- β is calculated as $\ln(1.26)/18.6 = 1.24 \times 10^{-2}$ $(\mu g/m^3)^{-1}$.
- The lifetime UR for 1-µg/m³ $PM_{2.5}$ is exp $(1.24 \times 10^{-2}) = 1.0125$, and the lifetime ACR is 20 times the coefficient of the UR, or 1.282 for 20-µg/m³ $PM_{2.5}$.

Comparison of Risks by Magnitude and Ratio

URs and ACRs can be compared between studies by considering their algebraic value and determining which risk is larger and the magnitude of the difference. Since the majority of URs and ACRs are close to 1, it is difficult to appreciate the difference in risk that is implied by the relatively small algebraic difference. For example, the ACR for $PM_{2.5}$ measured at the ambient exposure of 20 µg/m³ is 1.28, while the ACR for tobacco smoke measured at the ambient

(MON) 08. 13'01 10:20/ST. 10:01/NO. 3560638488 P 7/21
FROM ISI DOCUMENT SOLUTIONS
PM3006519024
Source: https://www.industrydocuments.ucsf.edu/docs/nngj0001

exposure of 0.20 μg/m³ is 1.00002; their ratio is very close to 1.28, which masks the size of their relative potencies.

An alternative comparison is to consider the ratios of the β coefficients. Because URs and ACRs are close to 1.0, the β values are approximately equal to UR-1. Thus, β approximates the added risk (the risk added to the risk at zero exposure), and the ratio of the β factors is the ratio of the added risks. For the example given, the β factors for $PM_{2.5}$ and tobacco smoke are 0.247 and 1.80×10^{-5}, so the ratio is 13,722. This indicates that the added risk from $PM_{2.5}$ is about 14,000 times larger than that from tobacco smoke at ambient concentrations. We will use this method of comparison in addition to comparing the magnitude of the ACRs, and we will denote it as the ratio of coefficients.

RESULTS

Background for PM and Smoking in Prospective Cohort Studies

The Six Cities and ACS studies assessed the association between $PM_{2.5}$, smoking, and mortality using Cox proportional-hazards regression models. The value used to estimate ambient exposure was the average of the reported ACS and Six Cities annual $PM_{2.5}$ concentration means. The former was based on 4 years of observed data, the latter on 16 years of observed data. In the AHSMOG cohort, 26 years of data on PM_{10} were available. The annual average is equivalent to lifetime intensity of exposure.

The RRs of smoking were assessed in each of the PM studies and are used to test the PM hypothesis, since tobacco smoke is a constituent of ambient air as well as a very important source of home, work, and personal exposure. Sidestream smoke is inhaled by smokers and nonsmokers alike and is called ETS. Gori and Mantel[9] estimate that ETS-attributable PM concentrations generally are less than 50 μg/m³. The National Research Council[9] estimates that ETS concentrations range from 20–150 μg/m³ in homes of smokers. Approximately 90% of the general population as well as the PM cohort populations are exposed to tobacco smoke whether they smoke or not. Klepeis[10] estimated average exposure to ETS is about 18 μg/m³, a value comparable to the average outdoor concentrations in the Six Cities study. Thus, tobacco smoke is a major source of workplace and home $PM_{2.5}$ exposure among nonsmokers and a primary source of exposure to $PM_{2.5}$ for smokers.

Ambient ETS concentrations are less than home and workplace concentrations, but they are measurable. Rogge et al.[11] estimated the upper limit of ambient ETS concentration in Los Angeles was approximately 0.28–0.36 μg/m³, or 1–1.3% of $PM_{2.5}$ mass concentration. The contemporary ambient exposure concentration for ambient tobacco smoke concentrations is set at 0.2 μg/m³ (Table 1).

Results of ACR calculations from the PM cohort studies are presented below, for mortality from all causes, cardiopulmonary diseases, and lung cancer, and the ranges of ACRs are located in Table 2. Details are in the Appendix.

ACRs for All-Cause Mortality for PM and Cigarette Smoke

ACRs for Ambient PM. In the Six Cities cohort, the only significant elevated ACRs were for Steubenville, 1.28 (1.06–1.33) for the entire cohort and 1.32 (1.03–1.68) for men. The lowest ACR were 0.67 (0.01–49.5) for women in Topeka and 0.73 (0.20–2.55) for men in Watertown. The highest ACRs were 1.69 (0.04–60) for men in Topeka, 1.48 (0.92–2.41) for men in Harriman, 1.42 (0.79–2.49) for men in St. Louis, and 2.77 (0.69–11.5) and 1.36 (0.69–2.76) for women in Watertown and St. Louis, respectively (Figure 2). There was no consistent E-R trend for men or women when considered separately. For example, in Topeka the men had the highest ACR and the women the lower, while the reverse was true in Watertown. The linear relationship seen in Figure 3 of Dockery et al.[2] is apparent when men and women are combined, but not apparent when considered separately.

In the ACS cohort, the ACRs for total mortality were about 1.14 for both men and women. In the AHSMOG cohort, all-cause mortality was not associated with PM_{10} for either men or women with ACRs of 1.09 (0.98–1.21) for men and 0.95 (0.87–1.03) for women (Figure 2).

ACRs for Cigarette Smoke. In the Six Cities cohort, the ACR of all-cause mortality for cigarette smoke was 1.00001 compared to an ACR of 1.28 per 20-μg/m³ $PM_{2.5}$. The ratio of the coefficients is an implausibly large 25,000. In ACS, the ratio of the coefficients is about 4000. At ambient concentrations of ETS, the ACRs for cigarette smoke are too low to detect with any reliability. No data were provided on risk of all-cause mortality in AHSMOG. The ratios of ACR coefficients (PM/tobacco smoke) show the group-level PM risks are 3 or more orders of magnitude larger than the individual-level estimated risks associated with ambient tobacco smoke (Table 3).

ACRs of Cardiopulmonary Mortality for PM and Tobacco Smoke

ACRs for Ambient PM. The ACR for cardiopulmonary mortality in the Six Cities cohort is 1.4 (1.12–1.75). The association of NMRD and $PM_{2.5}$ was unstable and statistically nonsignificant. When cardiovascular and respiratory disease deaths were combined, the associations with air pollution became consistent and robust.

In the ACS cohort, the ACR for cardiopulmonary mortality was 1.25 (1.14–1.36) for the entire cohort, but

FROM ISI DOCUMENT SOLUTIONS (MON) 08. 13' 01 10:21/ST. 10:01/NO. 3560638488 P 8/21

PM3006519025

Source: https://www.industrydocuments.ucsf.edu/docs/nngj0001

Table 2. Range of ACRs for PM cohort studies

Cause of Death	High ACRs (CI)	Low ACRs (CI)
All-cause mortality	2.77 (0.69–11.5) women, Watertown	0.67 (0.01–49.5) women, Topeka
Total cohort	1.32 (1.03–1.68) men, Six Cities	0.95 (0.87–1.03) women, AHSMOG
Cardiopulmonary	1.40 (1.12–1.75) Six Cities	0.93 (0.83–1.04) women, AHSMOG
NMRD	1.19 (0.95–1.49) men, AHSMOG	No association in Six Cities; 1.08 (0.88–1.32) for women in AHSMOG
Lung cancer	3.96 (1.74–9.01) men, AHSMOG (Beeson et al.[4])	0.92 (0.62–1.35) women, ACS

less for men (1.19) than for women (1.36). The separate effects of NMRD are not provided, although the total number of deaths in this cohort is 20,765 compared with 1430 in the Six Cities cohort. Separate results for respiratory and cardiovascular disease deaths as in AHSMOG would be useful in both Six Cities and ACS to better assess inter-study consistency and external comparisons with occupational cohorts.

The AHSMOG cohort considered cardiopulmonary and NMRD causes of death separately. There were no associations between cardiopulmonary deaths and any of the air pollutants for either sex. ACRs for PM_{10} and cardiopulmonary mortality were 1.08 (0.95–1.24) for men and 0.93 (0.83–1.04) for women (Figure 3). The 135 deaths from NMRD as an underlying cause showed no significant associations with PM_{10}, although a reduced model gave an ACR risk of 1.12 (0.84–1.50) for men. Causes of death with any mention of NMRD had ACRs of 1.19 (0.95–1.49) for men, 1.08 (0.88–1.32) for women, and 1.13 (0.975–1.31) for combined men and women. Thus, in AHSMOG the ACRs for NMRD were higher than for cardiovascular deaths, although none were significant.

ACRs for Tobacco Smoke. The ACRs for cardiopulmonary mortality and cigarette smoke were 1.0000 in both the Six Cities and ACS cohorts, with differences in toxicity based on the ratio of coefficients of about 11,000 and 7000, respectively (Table 3). ACRs of cigarette smoke in the AHSMOG cohort were 1.0000 for death with any mention of NMRD. They were not reported for cardiovascular mortality. These calculations suggest group-level PM risks of cardiopulmonary mortality are 3 or more orders of magnitude larger than individual-level estimated risks associated with ambient concentrations of tobacco smoke.

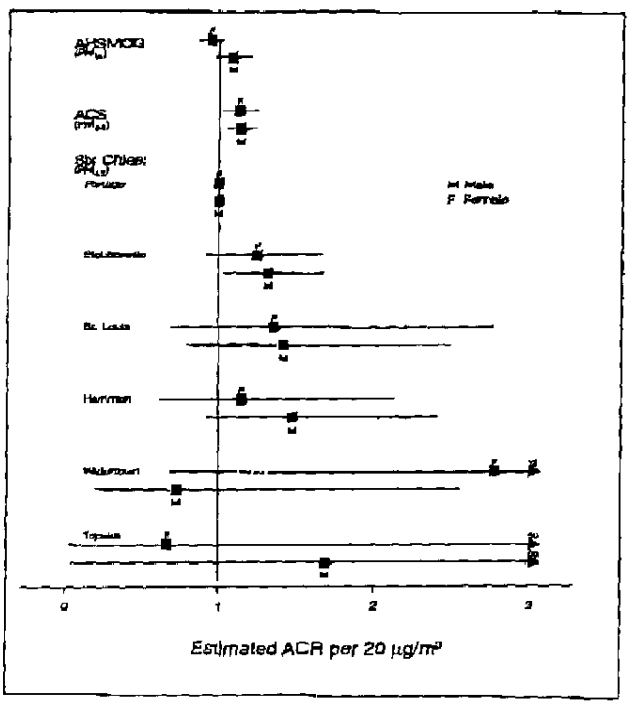

Figure 2. ACRs associated with all-cause mortality in PM cohort studies

ACRs for Lung Cancer Mortality for PM and Tobacco Smoke

ACRs for PM. The lung cancer ACR for $PM_{2.5}$ from the Six Cities cohort is 1.40 (0.80–2.46). The ACR for $PM_{2.5}$ in the ACS cohort is 1.10 (0.84–1.37) for men, 0.92 (0.62–1.35) for women, and 1.02 (0.83–1.26) overall. Men in AHSMOG show lung cancer ACRs for PM_{10} of 2.74 (1.45–5.15)[3] or 3.96 (1.74–9.01).[4] Only the former is plotted in Figure 4. The ACR for PM_{10} among women was 1.27 (0.65–2.46) in Abbey et al.,[3] while Beeson et al.[4] only reported that for women, the 95% confidence intervals included the null value.

ACRs for Smoking. The lung cancer ACRs for PM in tobacco smoke were 1.0001 among current smokers in the ACS and Six Cities cohorts and 1.00003–1.00004 for former smokers in the three cohorts (Figure 4). The ratio of coefficients was ~4000 in Six Cities and 220 in ACS. In AHSMOG, the ratio of coefficients was ~34,000–46,000 for men and 6000 for women (Table 3). These calculations

FROM ISI DOCUMENT SOLUTIONS (MON) 08. 13' 01 10:22/ST. 10:01/NO. 3560638488 P 9/21

PM3006519026

Source: https://www.industrydocuments.ucsf.edu/docs/nngj0001

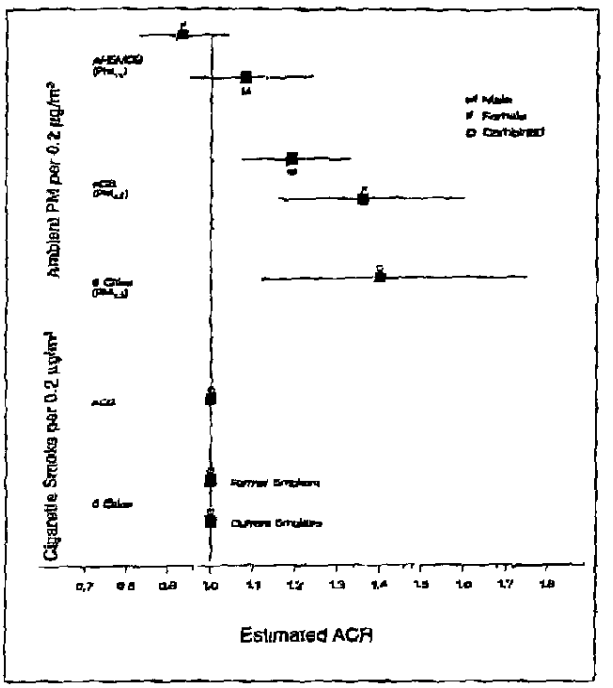

Figure 3. ACRs associated with cardiopulmonary mortality in PM cohort studies.

suggest group-level PM risks of lung cancer are 2 or more orders of magnitude larger than estimated individual-level risks associated with ambient concentrations of tobacco smoke.

Occupational Cohort Studies

Results are presented below for ACRs derived from occupational studies. Analyses were conducted for five categories of occupational exposures: (1) carbon black; (2) diesel exhaust; (3) PAHs including benzo(a)pyrene (BaP); (4) transition metals (As, Cr, and Ni); and (5) SiO_2; and analyses were performed for all causes, cardiovascular, respiratory, and lung cancer mortality. These are described below, and each section includes background information about the exposures and the studies selected for analyses. The ACRs are displayed in Figures 5–8 and summarized in Table 4. Also included in Table 4 are the ACRs for smoking, which were discussed previously and are included here to provide a more complete listing of individual level ACRs. More detailed information is in the Appendix.

Carbon Black. The amount of carbon black in ambient air is small. A study in 1969 estimated tire dust (of which carbon black is a component) constituted 0.8% of the aerosol above urban air in California.[12] Maximum PM_{10} in the AHSMOG study is about 80 µg/m³ with a minimum of zero. Therefore, carbon black in ambient air using these numbers would range from −0.008 to 0.66 µg/m³. The ACRs are calculated on the basis of 0.3 µg/m³ or 300 ng/m³.

Only one study was found that provided E-R trends, and trends for morbidity rather than mortality. Robertson and Ingalls[13] conducted a case-control study of carbon black workers 15 years of age or older employed in 1980 in all seven carbon-black plants in the United States.

The high-exposure category was >300-µg/m³ months cumulative exposure or a lifetime intensity of 357 µg/m³. The range of lifetime intensities was from no exposure to ~600 µg/m³. The lifetime intensities of cases and controls were similar and risks per 0.3 µg/m³ were 1.00 or less. ACRs for both cardiovascular and respiratory morbidity were at unity. Thus, the ACRs and ratio of coefficients for PM to carbon black are similar to those of PM to tobacco smoke.

Diesel Exhaust. Diesel exhaust concentrations in the Los Angeles area in the 1980s were estimated to account for ~3% of total PM emissions and 7% of respirable fine particles (PM_2) emissions. Average monthly ambient concentrations were estimated to range from 10 µg/m³ at the most polluted locations to 2–3 µg/m³ at less polluted areas.[14] Steenland et al.[15] assumed a background of 1 µg/m³. The EPA[16] estimated annual averages for the United States as 1.5–1.8 µg/m³ for 1990 and 1.1–1.2 µg/m³ for 1995. The estimates for calculating ACRs are based on an average ambient concentration of 1 µg/m³, and so they are equivalent to UR.

Three studies were used to estimate ACRs. Two were cohort mortality studies of coal miners and potash miners with internal analyses comparing exposed to nonexposed miners.[17,18] The third study was a case-control study of truck

Table 3. Ratio of coefficients[a] for PM and smoking.

Cause of Death	Six Cities	ACS	AHSMOG
All-cause mortality	25,000[b]	4400	N.A.[b]
Cardiopulmonary	11,000	7400	N.A.
NMRD	N.A.	N.A.	Men = 18,200 Women = 13,100
Lung cancer	≈200	220	Men = 34,000–46,000 Women = 8000

Note. [a]A sample calculation of the ratio of coefficients using Six Cities and all-cause mortality. The ACRs for $PM_{2.5}$ are 1.28, and for tobacco smoke they are 1.00001. The ratio of ACR coefficients is (1.28/n 1.00001 = 0.2469/0.00001 = 24,695, which is rounded off to 25,000. [b]N.A. = not available.

FROM ISI DOCUMENT SOLUTIONS
(MON) 08. 13' 01 10:22/ST. 10:01/NO. 3560638488 P 10/21
PM3006519027
Source: https://www.industrydocuments.ucsf.edu/docs/nngj0001

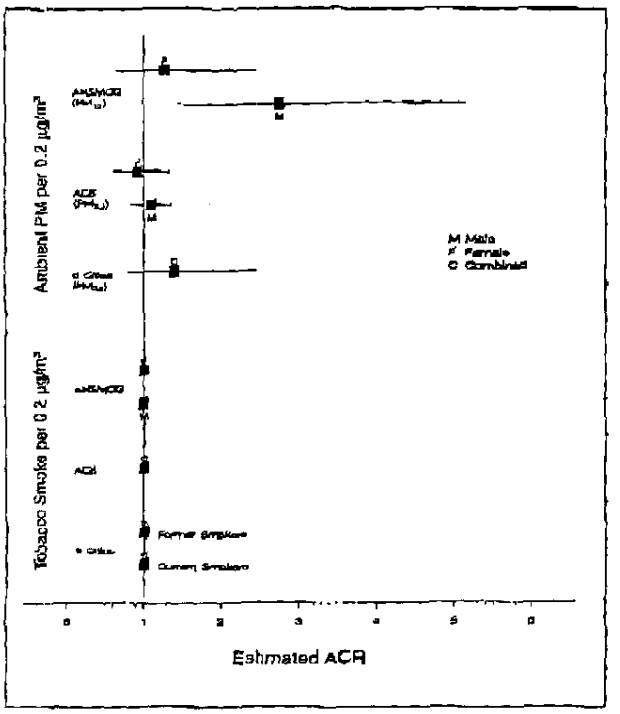

Figure 4. ACRs associated with lung cancer in PM cohort studies.

drivers.[14] ACRs were generally near 1.0 for all mortality outcomes, so the ACRs and ratios of coefficients are similar to the results for tobacco smoke.

PAHs. PAHs are ubiquitous air pollutants largely formed from the incomplete combustion of fossil and biogenic fuels. Concentrations of particle-bound PAHs in ambient air typically range from less than 1 µg/m³ in rural areas to 1–10 µg/m³ in urban areas.[19] Ambient concentrations of BaP are considerably lower: <1 ng/m³ in urban areas without coke ovens, 1–5 ng/m³ in other cities, and 100 ng/m³ in several European cities in the 1960s.[20] Hemminki and Pershagen[21] indicate mean concentrations of 0.7 ng/m³ of PAHs as BaP in Sweden. The Expert Panel on Air Quality Standards[22] reported annual means in the United Kingdom that ranged from ~2 ng/m³ or less in 1991 to 0.5–0.8 ng/m³ in 1998. Rural levels were on the order of 0.1–0.3 ng/m³ or less. ACRs for PAHs and BaP are based on average ambient concentrations of 5 µg/m³ and 2 ng/m³ (0.002 µg/m³), respectively.

Two occupational settings are considered for assessing E-R between mortality and exposure to coal tar pitch volatiles, namely, alumina reduction plants and coke ovens. Three studies were found with E-R analyses, including two in the coke ovens.[23,24] The coke oven workers appear to be the same cohort, and only the Costantino et al. data[23] will be used, since this is the latest update. Lung cancer mortality was assessed by Armstrong et al.[25] in a study of aluminum production workers.

Estimates of the ACRs from all the PAH studies showed similar results that were at unity and are, therefore, similar to the results for tobacco smoke.

Transition Metals. Spengler and Thurston[26] reported nondetectable concentrations of Ni in $PM_{2.5}$ fractions in three of the Six Cities—Portage, Topeka, and Harriman. Total concentrations of Ni in both the $PM_{2.5}$ and inhalable fraction (2.5–15 µm) ranged from a low of 0.0001 µg/m³ in Topeka to a high of 0.0195 µg/m³ in Watertown.

Time-series sample of trace metals were collected for several years in Philadelphia (n = 1105) and Phoenix (n = 643).[27] The average results were 0.00095 µg/m³ for As, 0.00055 µg/m³ for Cr, and 0.0038 µg/m³ for Ni, which are the units of exposure used in this review.

Costa[28] suggests that the "metal hypothesis" may be useful in explaining the epidemiologic findings of PM-associated mortality and morbidity. It is his view that "transition metals provide the foundation for biological plausibility." So it is useful to test the plausibility of this hypothesis.

Three studies were used to estimate ACRs. Two were cohort mortality studies of smelter workers exposed to As[29–31] and one was a multi-center study of welders exposed to Cr and Ni.[32] All ACR estimates for these studies were at unity, again similar to the ACRs for tobacco smoke.

Table 4. Range of ACRs in occupational studies and for tobacco smoke per average concentrations in ambient air

Exposure	All Cause	Cardiovascular	Respiratory	Lung Cancer
Carbon black morbidity	N A[a]	0.998	1.00000	N A
Diesel exhaust	0.991–1.001	0.998	1.018	0.982–1.16
PAHs	0.999–1.001	1.0005	1.0025	1.0005–1.04
BaP	N A	N A	N A	1.0003–1.003
As	N A	1.0000	N A	1.0000
Cr	0.99999	1.000	0.9999	1.000
Ni	0.9999	0.9999	0.996	1.000–1.001
SiO_2	1.003–1.015	0.988–1.02	1.04–2.14	0.82–1.23
Cigarette smoke	1.00001–1.00003	0.99927–1.003	1.00000	1.00003–1.01365

Note: [a]N A = not available

FROM ISI DOCUMENT SOLUTIONS (MON) 08. 13' 01 10:23/ST. 10:01/NO. 3560638488 P 11/21
PM3006519028
Source: https://www.industrydocuments.ucsf.edu/docs/nngj0001

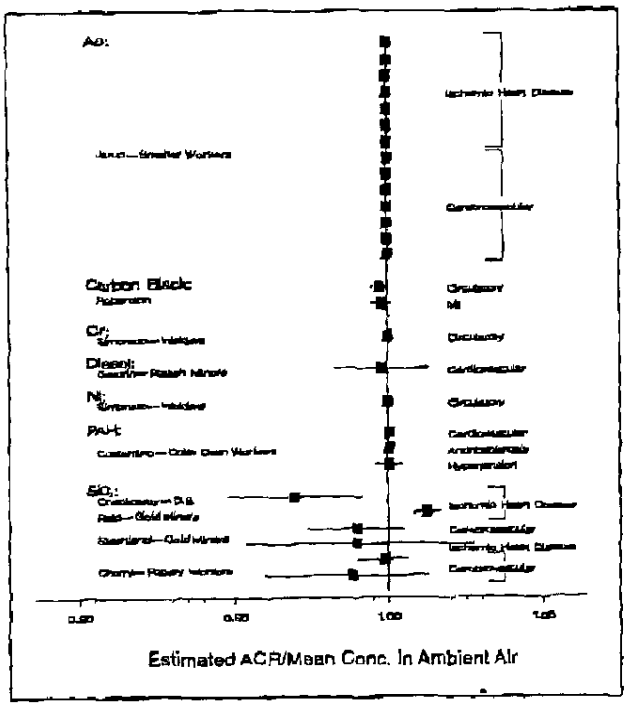

Figure 5. ACRs associated with all-cause mortality in occupational studies stratified by constituents in ambient air

Inorganic Dusts (SiO_2). Samples collected in the Six Cities cohort over about a 2-year period showed SiO_2 concentrations in the $PM_{2.5}$ fraction that varied from a low of 0.075 μg/m³ in Portage to a high of 0.29 μg/m³ in Steubenville.[26] Concentrations in the coarse fraction (size 2.5–15 μm) ranged from 0.98 μg/m³ in Portage to 2.5 μg/m³ in Topeka. The combined SiO_2 concentrations ranged from 1.06 μg/m³ in Portage to highs of 2.59 μg/m³ in Steubenville and 2.69 μg/m³ in Topeka. The SiO_2 content from time-series samples in Philadelphia and Phoenix ranged from 0.116 to 0.209 μg/m³ (0.0068–0.022%).[27] The average concentration was 0.105 μg/m³ (0.01%). In the 1996 Criteria Document, the EPA[1] indicated that the average concentration of SiO_2 was 4.9% in coarse PM and 0.4% in fine PM. When these percentages are applied to the AHSMOG data, the annual concentrations of SiO_2 ranges from about 0.05 to 4.4 μg/m³. An average SiO_2 concentration in ambient air of 3 μg/m³ is the value used for estimates of the ACRs.

Seven occupational studies were found for analyses. These include a mortality study of workers processing diatomaceous earth,[34] three studies of gold miners,[35–37] and three studies of workers in pottery/quarry/mining types of work.[38–40]

Some of these studies had statistically significant ACRs above 1.0 (e.g., studies of gold miners). Three SiO_2 studies showed ACRs of ~1.02 or less for total mortality. There was one study with an ACR of 1.01 for cerebrovascular and ischemic heart disease mortality. The ACR was 1.04 for chronic obstructive pulmonary disease (COPD) mortality among South African gold miners. The greatest risk in the occupational cohorts was associated with lung cancer, but at ambient concentrations, the ACRs are also around unity with few exceptions.

DISCUSSION

We have summarized the results from a series of E-R studies assessing the associations of mortality with ambient PM, with individual-level exposures to tobacco smoke and various occupational exposures. Comparisons of ACRs from these studies provide the data for answering the two questions posed at the outset of this analysis.

Tests of Internal Consistency

All-Cause Mortality (see Figure 2). The ACS cohort shows consistent and significant ACRs of ~1.14 per 20-μg/m³ $PM_{2.5}$ for total mortality in both sexes. However, these results do not appear to be consistent with two of the Six Cities or AHSMOG.

The comparative statistics usually given for the Six Cities cohort when calculated as ACRs are 1.32 for men and 1.25 for women. However, when assessed by city, the ACRs varied for men from 0.73 in Watertown to 1.69 in Topeka. For women, the range was 0.67 in Topeka to 2.77 in Watertown. Thus, the risks associated with total mortality do not increase monotonically with estimated PM for each city; they show an inverse pattern for men and women in two of the six cities (Topeka and Watertown), and the most polluted city (Steubenville) has lower ACRs than cities with less pollution (Topeka, Harriman, and St. Louis for men; Watertown and St. Louis for women). All-cause mortality is not significantly increased in the AHSMOG cohort, and the ACR is <1 for women.

Cardiopulmonary and Respiratory Mortality. The ACS results show increased risks for cardiopulmonary mortality that are greater for women than men (Figure 3). In Six Cities, results showed greater risk for cardiovascular than respiratory mortality. These results are inconsistent with AHSMOG, where the risk is greater for respiratory than cardiovascular mortality and greater for men than for women.

FROM ISI DOCUMENT SOLUTIONS (MON) 08. 13' 01 10:23/ST. 10:01/NO. 3560638488 P 12/21
PM3006519029
Source: https://www.industrydocuments.ucsf.edu/docs/nngj0001

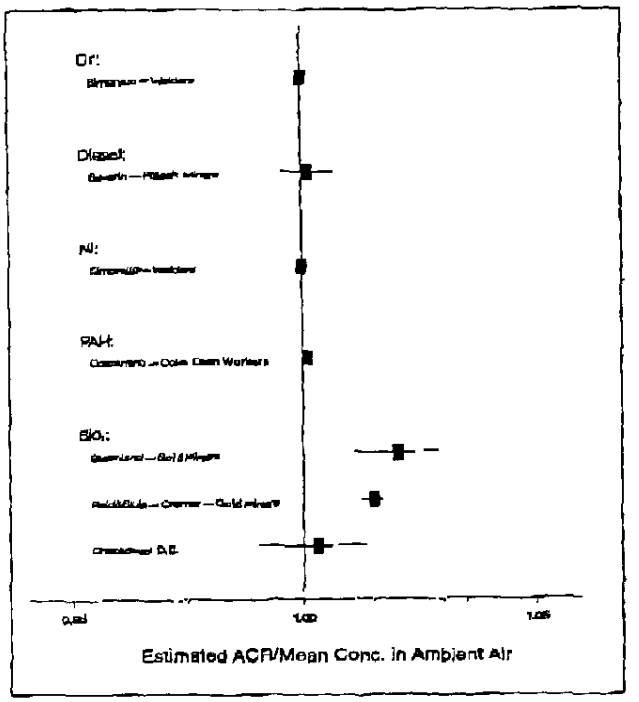

Figure 6. ACRs associated with cardiovascular mortality in occupational studies stratified by constituents in ambient air.

Lung Cancer. Six Cities and AHSMOG show increases in risk of lung cancer that are inconsistent with the lack of risk in ACS. The ratios of coefficients for lung cancer for men and women combined was 17 times greater in Six Cities than in ACS, and 11 times greater for men in AHSMOG than in ACS. The ACR for women in ACS was less than 1, but was 1.27 in AHSMOG.

The lung cancer results are perplexing, as there is no apparent increased risk in ACS, an increased but not significantly increased risk in Six Cities, and in AHSMOG a large increased risk for women and an even larger and more implausible risk for men (2.74 in Abbey et al.[3] and 3.96 in Beeson et al.[2]).

These analyses suggest that the results from the three PM cohorts are not qualitatively similar. While there are significant associations in one or more of the studies, at least one of the three generally has results that do not appear to be congruent with the other two, and the outlying study is different depending on the cause of death.

If there is no consistency within or between the PM studies, what ACRs should be used for comparisons to smoking and occupational data? The choices are reasonably limited to the maximum ACR, the minimum ACR, or some average measure such as the arithmetic mean or geometric mean. We will use the minimum and maximum ACRs for each mortality end point, as summarized in Table 2.

Test of External Consistency

Smoking. The ACRs for cause-specific deaths associated with smoking ranged between 1.00001 and 1.00009. The results are quite consistent for men and women, former and current smokers, and between cohorts for all causes of death.

In addition, the ratio of coefficients for PM versus tobacco smoking is 2–4 orders of magnitude, as shown in Table 3. The exception is the ACS cohort, where the risk of lung cancer was not increased.

If the lower PM ACRs are used, they are generally less than 1 (Table 2), which indicates they are not toxic (it is not reasonable to call them protective). Thus, in comparison to tobacco smoke, whose ACRs are very slightly greater than 1 (Table 4), and based on the lower estimated PM risks, ambient PM can be considered nontoxic at ambient concentrations used in this analysis.

Tobacco smoke is known to be a significant risk factor for all causes of death studied in the air pollution cohorts, but in the PM cohort studies, the ACRs for tobacco smoke are equivalent to a value of 1.0000, indicating no toxicity at ambient concentrations. Thus, in the PM cohort studies, the ability to detect meaningful risks at ambient concentrations of ETS is essentially none. The inability to reliably measure ACRs for ETS detracts from the PM hypothesis. The results for tobacco exposure are not coherent with the high URs associated with PM from the air pollution studies, but they are coherent with the lack of risk seen for the low ACRs associated with ambient PM.

In summary, there is a lack of coherence when comparing the higher ACRs derived from ambient PM with the ACRs derived from tobacco smoke. The ratios of coefficients comparing higher PM risk estimates with tobacco smoke are so large as to not be plausible. The lower risk estimates derived from ambient PM are less than the ACRs for smoking, and do not suggest a causal association, as these low ACRs indicate no association with mortality. At the average concentrations measured in ambient air in these studies, ambient PM is either more toxic than similar concentrations of tobacco smoke (based on the higher ACRs), or somewhat less toxic than tobacco smoke so reliable estimates of risk cannot be detected at these concentrations (using lower ACRs).

The results using tobacco smoke suggest the consistency and coherence criteria for a causal association

(MON) 08. 13' 01 10:24/ST. 10:01/NO. 3560638488 P 13/21
FROM ISI DOCUMENT SOLUTIONS
PM3006519030
Source: https://www.industrydocuments.ucsf.edu/docs/nngj0001

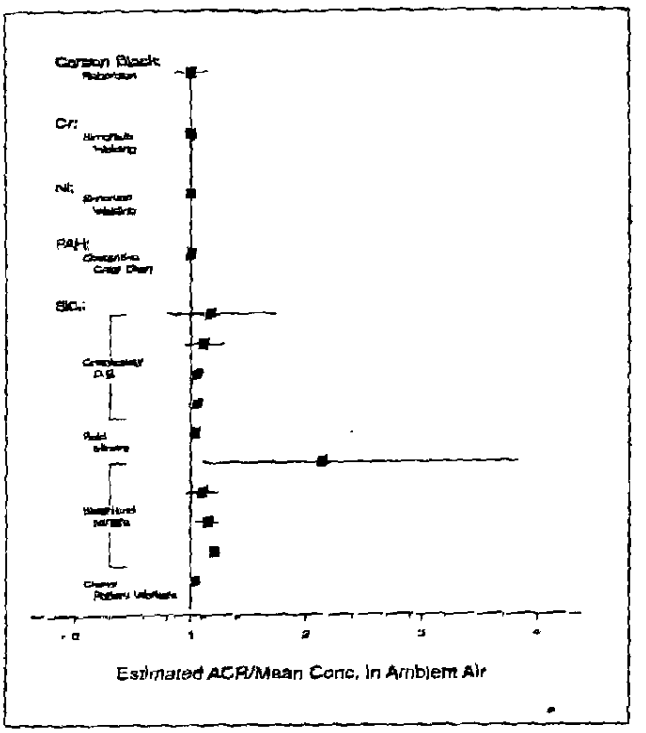

Figure 7. ACRs associated with respiratory mortality in occupational studies stratified by constituents in ambient air

between PM and mortality in the Six Cities, ACS, and AHSMOG cohorts are not met, and the lower ACRs for $PM_{2.5}$ and PM_{10} are the more plausible.

Occupational. Occupational studies with quantitative E-R analyses were summarized where the major occupational exposure was a particulate constituent of urban air, namely, carbon black, diesel exhaust, PAHs, BaP, Cr, As, Ni, and SiO_2. All of these substances, with the possible exception of carbon black, have been considered as possible or probable substances causing cardiopulmonary disease and/or lung cancer at some concentration.

The results of the occupational studies are consistent among themselves for all causes of death and for each pollutant. The ACRs are consistently about 1.00, as summarized in Table 4 and shown in Figures 5–8, with a few above 1.0 and more below 1.0, and with few exceptions are similar to the ACRs for tobacco smoke.

At these low ACRs, one would not be able to detect an increased risk of mortality with any degree of reliability. These low ACRs also indicate that exposures to these substances at ambient concentrations are not toxic.

An ACR of at least 1.0 should be expected, as positive E-R trends are common. When the E-R is analyzed by regression, a linear model is generally the method of choice, which assumes no threshold. Thus, if there is an E-R trend, then the coefficient will be positive, even at the comparatively low concentrations in ambient air compared to workplace exposures. And one would expect positive E-R trends for several reasons, including the toxic nature of most of these substances at some concentration, increased potential for increased risks at high intensities, and possible underestimates of exposure in the past that can produce an overestimate in toxicity.

Most occupational ACRs are ~1.0 for all cause-specific mortality, although a few ACRs are higher. For example, the SiO_2 studies generally show increased mortality for respiratory diseases, and especially for silicosis, but often do not for other causes of death. The highest SiO_2 ACRs are 1.02 for total and cardiovascular mortality, but are 2.14 for respiratory and 1.23 for lung cancer mortality. In contrast, the highest PM-based ACRs by cause of death are 2.77 for women in Watertown, 1.40 for Six Cities, 1.19 for men in AHSMOG, and 3.96 for men in AHSMOG (Table 2). Using the ratios of the ACR coefficients, the estimated toxicity of PM at ambient concentrations is 14 times greater than SiO_2 for total mortality, 17 times greater for cardiopulmonary, and 7 times greater for lung cancer. The estimate for respiratory mortality is about 4 times greater for SiO_2 than for PM.

Considering the results by cause of death, the ratio of coefficients between the PM and occupational/smoking estimates of risks have a broad range. When the ratios are near unity, they are generally associated with risks less than 1 from both sources. As an example, all of the lowest ACRs for PM are less than 1.0, so the ratios are all less than 1.0, indicating that ambient PM is less toxic than all the occupational exposure agents at ambient concentrations. Some might argue that occupational cohorts are not suitable for comparison with the PM cohorts because of the healthy worker effect and the need to protect susceptible individuals. In many of these studies, there was no apparent healthy worker effect as total and cause-specific mortality were often near or above the null value.

The AHSMOG cohort was selected as a low-risk group. It is compulsed of Seventh-Day Adventists, a group whose religion prohibits the use of alcohol, tobacco, and pork and strongly recommends a lacto-ovovegetarian diet. Earlier reports documented their lower mortality for cancer, cardiovascular, and other chronic diseases compared with the U.S. population and nonsmoking

FROM 1ST DOCUMENT SOLUTIONS
(MON) 08. 13' 01 10:25/ST. 10:01/NO. 3560638488 P 14/21
PM3006519031
Source: https://www.industrydocuments.ucsf.edu/docs/nngj0001

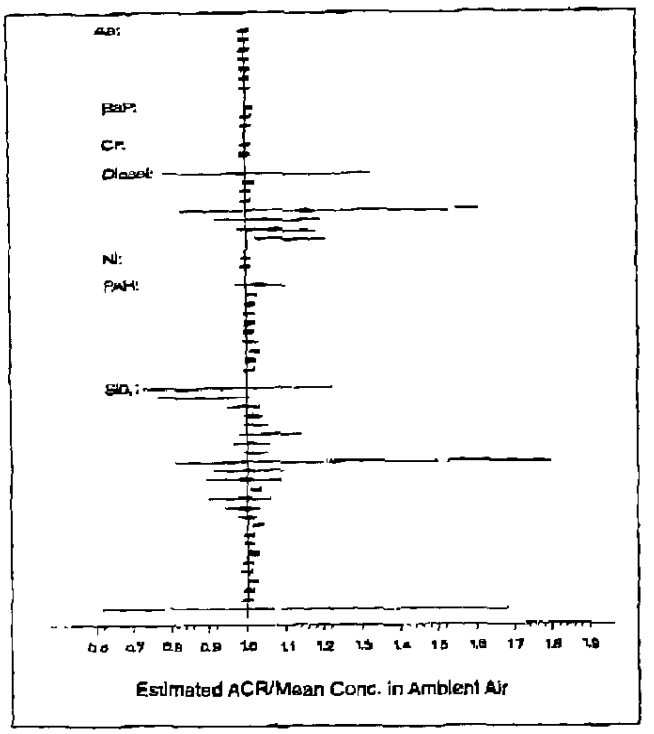

Figure 8. ACRs associated with lung cancer mortality in occupational studies stratified by constituents in ambient air.

whites living in California.[1] So this population appears to be a healthy population, perhaps more so even than an occupational cohort.

The ACS cohort is also likely to be a healthy population. It is not representative of the general population, but "was >90% white, mainly middle class, older, more educated, more often married, and less urban".[44] Except for age, which is controlled in the analysis, these tend to be factors that are associated with better rather than poor health.

The weight of evidence from the occupational cohorts, like that from smoking, suggests that PM ACRs are implausibly high. Further, the ACRs estimated from these occupational toxicants are unlikely to be detected with reliability, even though the risks are consistently elevated at the concentrations found at work.

Strengths and Limitations of Analyses

The analytic approaches used in this paper have both advantages and possible limitations. First, ACR comparisons for each substance (e.g., tobacco smoke and PAHs) were made at current estimates of ambient exposures. This is a different way to compare risks, and is in contrast to a more traditional UR approach of using a fixed unit for each substance, such as 1 $\mu g/m^3$. When considering large differences in toxicity between substances, the fixed UR approach sometimes creates highly unrealistic scenarios (e.g., a level of exposure that would be extremely toxic), compared with the ambient level comparisons, where the concentrations are so low that a response as severe as mortality cannot be measured with reliability.

The smoking comparisons utilize data from the same three cohort studies from which the PM estimates came. These data provide two estimates of ACRs for the same individuals in the same study, thereby providing scientifically robust, within-study comparisons of risk contrasting group-level exposure (ambient PM) and exposures to tobacco smoke, which are estimated at the individual level. The comparisons to occupational studies are not as robust since the populations are not the same people and the risks are derived from different studies at different exposures and perhaps different particle sizes. However, the weight of evidence from occupational studies shows a consistency of results across many studies and different substances, and the ratios of risks are so large as to make it improbable that the problems in the occupational comparison could be explained by those relatively minor differences. It is also improbable that the differences in categories for cardiopulmonary mortality can explain the differences in risk. Thus, these comparisons indicate a lack of coherence between risks derived from ambient PM studies and those from occupational studies.

Our analyses have assumed a no-threshold model for the E-R. We have also assumed the E-R relationship holds over the range of high occupational exposures to low ambient exposures. These methods have some uncertainties, but the techniques are generally accepted. However, regarding both of the assumptions above, other approaches should be tried and compared to our findings.

CONCLUSIONS

(1) There is a lack of intra- and inter-study consistency in the results from the air pollution cohorts that detracts from the PM hypothesis.

(2) There is a lack of coherence between higher PM ACRs and ACRs derived from individual-level estimates of exposure, so the hypothesis of a causal association between ambient PM and chronic mortality is not supported.

(3) Current concentrations of several kinds of PM in ambient air (e.g., tobacco smoke, diesel exhaust,

FROM ISI DOCUMENT SOLUTIONS (MON) 08. 13'01 10:25/ST. 10:01/NO. 3560638488 P 15/21

PM3006519032

Source: https://www.industrydocuments.ucsf.edu/docs/nngj0001

PAHs, and transient metals) are too low to reliably measure risks of mortality.

(4) The lower PM ACRs are similar to individual-level ACRs, indicating that concentrations of PM in the Six Cities, ACS, and AHSMOG studies are too low to estimate risks of mortality, and that higher ACRs for PM are probably overestimates of the true risks.

ACKNOWLEDGMENTS

We acknowledge the support of CONCAWE and the extra effort of Wendy Huebner, Laurie Mackenzie, Chris Phillips, and Nancy Wojcik to meet the deadlines for submission.

REFERENCES

1. Pope, C.A.; Thun, M.J.; Namboodiri, M.M.; Dockery, D.W.; Evans, J.S.; Speizer, F.E.; Heath, C.W. Particulate Air Pollution as a Predictor of Mortality in a Prospective Study of U.S. Adults; *Am. J. Respir. Crit. Care Med.* 1995, *151*, 669-674.
2. Dockery, D.W.; Pope, C.A., Xu, X.; Spengler, J.D.; Ware, J.H.; Fay, M.E.; Ferris, B.G.; Speizer, F.E. An Association between Air Pollution and Mortality in Six U.S. Cities; *N. Engl. J. Med.* 1993, *329*, 1753-1759.
3. Abbey, D.E.; Nishino, N.; McDonnell, W.F.; Burchette, R.J., Knutsen, S.F.; Beeson, W.L.; Yang, J.X. Long-Term Inhalable Particles and Other Air Pollutants Related to Mortality in Nonsmokers; *Am. J. Respir. Crit. Care Med.* 1999, *159*, 373-382.
4. Beeson, W.L.; Abbey, D.E.; Knutsen, S.F. Long-Term Concentrations of Ambient Air Pollutants and Incident Lung Cancer in California Adults: Results from the AHSMOG Study; *Environ. Health Perspect.* 1998, *106*, 813-823.
5. Oxman, A.D.; Muir, D.C.F.; Shannon, H.S.; Stock, S.R.; Hnizdo, E.; Lange, H.J. Occupational Dust Exposure and Chronic Obstructive Pulmonary Disease. A Systematic Overview of the Evidence; *Am. Rev. Respir. Dis.* 1993, *148*, 38-48.
6. Holland, C.D.; Sielken, R.L., Jr.; *Quantitative Cancer Modeling and Risk Assessment*; Prentice Hall: New York, 1993.
7. Seaton, A.; MacNee, W.; Donaldson, K.; Godden, D. Particulate Air Pollution and Acute Health Effects; *Lancet* 1995, *345*, 176-178.
8. Gori, G.B.; Mantel, N. Mainstream and Environmental Tobacco Smoke; *Regul. Toxicol. Pharmacol.* 1991, *14*, 85-105.
9. *Environment Tobacco Smoke: Measuring Exposures and Assessing Health Effects*; National Research Council; National Academy Press: Washington, DC, 1986.
10. Klepeis, N.E. An Introduction to the Indirect Exposure Assessment Approach; Modeling Human Exposure Using Microenvironmental Measurements and the Recent National Human Activity Pattern Survey; *Environ. Health Perspect.*, 1999, *107(Suppl. 2)*, 365-374.
11. Rogge, W.F.; Hildemann, L.M.; Mazurek, M.A.; Cass, G.R.; Simoneit, B.R.T. Sources of Fine Organic Aerosol. 6. Cigarette Smoke in the Urban atmosphere; *Environ. Sci. Technol.* 1994, *28*, 1375-1388.
12. *IARC Printing Processes and Printing Inks, Carbon Black and Some Nitro Compounds, Vol. 65*; Lyon, France, October, 1995; World Health Organization: Geneva, Switzerland, 1996.
13. Robertson, J.M.; Ingalls, T.H. A Case-Control Study of Circulatory, Malignant, and Respiratory Morbidity in Carbon Black Workers in the United States; *Am. Ind. Hyg. Assoc. J.* 1989, *50*, 510-515.
14. Cass, G.R.; Gray, H.A. *Regional Emissions and Atmospheric Concentrations of Diesel Engine Particulate Matter: Los Angeles as a Case Study in Diesel Exhaust: A Critical Analysis of Emissions, Exposure, and Health Effects*; Health Effects Institute: Cambridge, MA, 1995.
15. Steenland, K.; Deddens, J.; Stayner, L. Diesel Exhaust and Lung Cancer in the Trucking Industry: Exposure-Response Analyses and Risk Assessment; *Am. J. Ind. Med.* 1998, *34*, 220-228.
16. *Health Assessment Document for Diesel Emissions*; SAB Review Draft; EPA/600/8-90/057C; U.S. Environmental Protection Agency, U.S. Government Printing Office: Washington, DC, February 1998.
17. Johnston, A.M.; Buchanan, D.; Robertson, A.; Millet, B.G. *Investigation of the Possible Association between Exposure to Diesel Exhaust Particulate in British Coal Mines and Lung Cancer*; Institute of Occupational Medicine Report TM/97/08; Institute of Occupational Medicine: Edinburgh, United Kingdom, November 1997.
18. Saverin, R., Braunlich, A.; Dahmann, D.; Enderlein, G.; Heuchert, G. Diesel Exhaust and Lung Cancer Mortality in Potash Mining; *Am. J. Ind. Med.* 1999, *36*, 415-422.
19. *HEI Diesel Emissions and Lung Cancer: Epidemiology and Quantitative Risk Assessment, A Special Report of the Institute's Diesel Epidemiology Expert Panel*; Health Effects Institute: Cambridge, MA, June 1999.
20. World Health Organization (WHO). *Air Quality Guidelines for Europe*; European Series No. 23; WHO Regional Publications: Geneva, Switzerland, 1987.
21. Hemminki, K., Partshuyen, G. Cancer Risk of Air Pollutions: Epidemiologic Evidence; *Environ. Health Perspect.* 1994, *102 (Suppl. 4)*, 187-192.
22. *Polycyclic Aromatic Hydrocarbons*; Expert Panel on Air Quality Standards (EPAQS); University of Aberdeen: United Kingdom, 1998.
23. Mazumdar, S.; Redmond, C.; Sollecito, W.; Sussman, N. An Epidemiological Study of Exposure to Coal Tar Pitch Volatiles among Coke Oven Workers; *J. Air Pollut. Control Assoc.* 1975, *25*, 382-389.
24. Costantino, J.P.; Redmond, C.K.; Bearden, A. Occupationally Related Cancer Risk among Coke Oven Workers: 30 Years of Follow-Up; *J. Occup. Env. Med.* 1995, *37*, 597-604.
25. Armstrong, B.; Tremblay, C.; Baris, D.; Theriault, G. Lung Cancer Mortality and Polynuclear Aromatic Hydrocarbons: A Case-Cohort Study of Aluminum Production Workers in Arvida, Quebec, Canada; *Am. J. Epidemiol.* 1994, *139*, 250-262.
26. Spengler, J.D.; Thurston, G.D. Mass and Elemental Composition of Fine and Coarse Particles in Six U.S. Cities; *J. Air Pollut. Control Assoc.* 1983, *33*, 1162-1171.
27. *Air Quality Criteria for Particulate Matter*, Vol. 1; External Review Draft; EPA 600/P-95/002a; U.S. Environmental Protection Agency, U.S. Government Printing Office: Washington, DC, October 1995.
28. Costa, D.L. Ambient Particulate Matter: Is There a Toxic Role for Constitutive Transition Metals? *Stud. Environ. Sci.* 1998, *72*, 117-123.
29. Jarup, L., Pershagen, G.; Wall, S. Cumulative Arsenic Exposure and Lung Cancer in Smelter Workers: A Dose-Response Study; *Am. J. Ind. Med.* 1989, *15*, 31-41.
30. Lee-Feldstein, A. Cumulative Exposure to Arsenic and Its Relationship to Respiratory Cancer among Copper Smelter Employees; *J. Occup. Med.* 1986, *28*, 296-302.
31. Lee-Feldstein, A. A Comparison of Several Measures of Exposure to Arsenic; Matched Case-Control Study of Copper Smelter Employees; *Am. J. Epidemiol.* 1989, *129*, 112-121.
32. Simonato, L.; Fletcher, A.C.; Andersen, A.; Becker, N.; Chang-Claude, J.; Ferro, G.; Gerin, M.; Gray, C.N.; Hansen, K.S.; Kalliomaki, P.L.; Kurppa, K.; Langard, S.; Merlo, F.; Moulin, J.J.; Newhouse, M.L.; Peto, J.; Pukkala, E.; Skjaerg, B.; Wild, P.; Winkelmann, R.; Saracci, R. A Historical Prospective Study of European Stainless Mild Steel and Shipyard Welders; *Br. J. Ind. Med.* 1991, *48*, 145-154.
33. *Air Quality Criteria for Particulate Matter*; EPA/600/P-95/001aF; U.S. Environmental Protection Agency; U.S. Government Printing Office: Washington, DC, April 1996.
34. Checkoway, H.; Heyer, N.J.; Seixas, N.S.; Welp, E.A.; Demers, P.A.; Hughes, J.M.; Weill, H. Dose-Response Associations of Silica with Nonmalignant Respiratory Disease and Lung Cancer Mortality in the Diatomaceous Earth Industry; *Am. J. Epidemiol.* 1997, *145*, 680-688.
35. Reid, P.J.; Sluis-Cremer, G.K. Mortality of White South African Gold Miners; *Occup. Environ. Med.* 1996, *53*, 11-16.
36. Hnizdo, E.; Murray, J.; Klempman, S. Lung Cancer in Relation to Exposure to Silica Dust, Silicosis and Uranium Production in South African Gold Miners; *Thorax* 1997, *52*, 271-275.
37. Steenland, K.; Brown, D. Mortality Study of Gold Miners Exposed to Silica and Nonasbestiform Amphibole Minerals: an Update with 14 More Years of Follow-Up; *Am. J. Ind. Med.* 1995, *27*, 217-229.
38. Ulm, K.; Waschulzik, B.; Ehnes, H.; Guldner, K.; Thomasson, B.; Schwebig, A.; Nub, H. Silica Dust and Lung Cancer in the German Stone, Quarrying, and Ceramics Industries: Results of a Case-Control Study; *Thorax* 1999, *54*, 347-351.
39. McLaughlin, J.K.; Jing-Qiang, C.; Dosemeci, M.; Rong-An, C.; Reiqing, S.H.; Zhiey, W.; Hearl, F.J.; McCawley, M.A.; Blot, W.J. A Nested Case-Control Study of Lung Cancer among Silica Exposed Workers in China; *Br. J. Ind. Med.* 1992, *49*, 167-171.
40. Cherry, N.M.; Burgess, G.L.; Turner, S.; McDonald, J.C. Crystalline Silica and Risk of Lung Cancer in the Potteries Group. *Environ. Med.* 1998, *55*, 779-785.
41. Beeson, W.L.; Mills, P.K.; Phillips, R.L.; Andress, M.; Fraser, G.E. Chronic Disease among Seventh-Day Adventists, a Low-Risk Group: Rationale, Methodology, and Description of the Population; *Cancer* 1989, *64*, 570-591.
42. Scheidt, S. Changing Mortality from Coronary Heart Disease among Smokers and Nonsmokers over a 20-Year Interval; *Preventive Med.* 1997, *26*, 441-446.

About the Authors

John F. Gamble is an epidemiologist and Mark J. Nicolich is a statistician. They have been conducting applied research in health-related topics for several decades at Occupational and Public Health Division, ExxonMobil Biomedical Sciences Inc., 1545 Rte. 22, Annandale, NJ 08801.

FROM 1SI DOCUMENT SOLUTIONS (MON) 08. 13'01 10:25/ST. 10:01/NO. 3560638488 P 16/21

PM3006519033

Source: https://www.industrydocuments.ucsf.edu/docs/nngj0001

Source: https://www.industrydocuments.ucsf.edu/docs/nngj0001

APPENDIX

Agent	Author	End Point	Sex	Base ($\mu g/m^3$)	Exposure ($\mu g/m^3$)	Ambient ($\mu g/m^3$)	UR per $\mu g/m^3$ Beta	Beta LL	ACR/Ambient Beta UL	Risk	Conc. Risk LL	Risk UL
$PM_{2.5}$	citiesTope	total	male	11.0	12.50	2.00E+01	2.62E-02	−1.81E-01	2.05E-01	1.69000	0.04000	60.3000
$PM_{2.5}$	citiesTope	total	female	11.0	12.50	2.00E+01	−2.00E-02	−2.30E-01	1.95E-01	0.87000	0.01000	49.5000
$PM_{2.5}$	citiesTope	total	combined	11.0	12.50	2.00E+01	6.55E-03	−1.33E-01	1.43E-01	1.14000	0.07000	17.6000
$PM_{2.5}$	citiesW	total	male	11.0	14.90	2.00E+01	−1.57E-02	−8.05E-02	4.58E-02	0.73000	0.20000	2.55000
$PM_{2.5}$	citiesW	total	female	11.0	14.90	2.00E+01	5.09E-02	−1.86E-02	1.22E-01	2.77000	0.89000	11.5000
$PM_{2.5}$	citiesW	total	combined	11.0	14.90	2.00E+01	1.72E-02	−2.99E-02	6.33E-02	1.41000	0.55000	3.56000
$PM_{2.5}$	citiesHar	total	male	11.0	20.80	2.00E+01	1.96E-02	−4.17E-03	4.40E-02	1.48000	0.92000	2.41000
$PM_{2.5}$	citiesHar	total	female	11.0	20.80	2.00E+01	6.99E-03	−2.39E-02	3.78E-02	1.15000	0.62000	2.13000
$PM_{2.5}$	citiesHar	total	combined	11.0	20.80	2.00E+01	1.61E-02	−5.27E-03	3.85E-02	1.38000	0.90000	2.16000
$PM_{2.5}$	citiesSiLo	total	male	11.0	19.00	2.00E+01	1.75E-02	−1.18E-02	4.56E-02	1.42000	0.79000	2.49000
$PM_{2.5}$	citiesSiLo	total	female	11.0	19.00	2.00E+01	1.54E-02	−1.86E-02	5.08E-02	1.36000	0.69000	2.78000
$PM_{2.5}$	citiesSiLo	total	combined	11.0	19.00	2.00E+01	1.85E-02	−5.27E-03	3.85E-02	1.38000	0.90000	2.16000
$PM_{2.5}$	citiesStub	total	male	11.0	29.60	2.00E+01	1.39E-02	1.46E-03	2.50E-02	1.32000	1.03000	1.68000
$PM_{2.5}$	citiesStub	total	female	11.0	29.60	2.00E+01	1.12E-02	−4.17E-03	2.55E-02	1.25000	0.92000	1.67000
$PM_{2.5}$	citiesStub	total	combined	11.0	29.60	2.00E+01	1.23E-02	2.91E-03	1.49E-02	1.26000	1.06000	1.33000
$PM_{2.5}$	ACS	total	male	9.0	33.50	2.00E+01	8.55E-03	2.91E-03	1.08E-02	1.14000	1.06000	1.24000
$PM_{2.5}$	ACS	total	female	9.0	33.50	2.00E+01	5.11E-03	9.80E-04	1.12E-02	1.13000	1.02000	1.25000
$PM_{2.5}$	ACS	total	combined	9.0	33.50	2.00E+01	6.55E-03	3.38E-03	9.53E-03	1.14000	1.07000	1.21000
PM_{10}	AHSMOG	total	male	0.0	83.90	2.00E+01	4.31E-03	−1.01E-03	9.53E-03	1.09000	0.98000	1.21000
PM_{10}	AHSMOG	total	female	0.0	83.90	2.00E+01	−2.56E-03	−6.95E-03	1.48E-03	0.85000	0.87000	1.03000
CigSmX	6 Cities	total	combined	0.0	4762.00	2.00E-01	6.00E-05	3.50E-05	9.49E-05	1.00001	1.00001	1.00002
CigSmX	6 Cities	total	combined	0.0	3175.00	2.00E-01	8.99E-05	−2.00E-05	1.95E-04	1.00002	1.00000	1.00004
CigSmX	6 Cities	total	combined	0.0	3968.00	2.00E-01	7.00E-05	3.00E-05	6.50E-05	1.00001	1.00001	1.00001
CigSmC	6 Cities	total	combined	0.0	3952.00	2.00E-01	4.00E-05	2.00E-05	5.50E-05	1.00001	1.00000 1	00001
CigSmC	6 Cities	total	combined	0.0	3968.00	2.00E-01	4.00E-05	0.00E+00	8.49E-05	1.00001	1.00000	1.00002
CigSmC	6 Cities	total	combined	0.0	4960.00	2.00E-01	4.50E-05	3.00E-05	6.50E-05	1.00001	1.00001	1.00001
CigSmC	ACS	total	combined	21.0	4950.00	2.00E-01	1.45E-04	1.15E-04	1.80E-04	1.00003	1.00002	1.00004
$PM_{2.5}$	citiesStub	cardio	combined	11.0	29.60	2.00E+01	1.68E-02	5.67E-03	2.80E-02	1.40000	1.12000	1.75000
$PM_{2.5}$	ACS	cardio	male	9.0	33.50	2.00E+01	8.70E-03	3.38E-03	1.49E-02	1.19000	1.07000	1.33000
$PM_{2.5}$	ACS	cardio	female	9.0	33.50	2.00E+01	1.54E-02	7.42E-03	2.35E-02	1.36000	1.16000	1.60000
$PM_{2.5}$	ACS	cardio	combined	9.0	33.50	2.00E+01	1.12E-02	6.55E-03	1.54E-02	1.25000	1.14000	1.36000
CigSmC	ACS	cardio	combined	21.5	4960.00	2.00E-01	1.65E-04	1.20E-04	2.15E-04	1.00003	1.00002	1.00004
PM_{10}	AHSMOG	cardio	male	0.0	83.90	2.00E+01	3.45E-03	−2.56E-03	1.08E-02	1.08000	0.95000	1.24000
PM_{10}	AHSMOG	cardio	female	0.0	83.90	2.00E+01	−3.63E-03	−9.32E-03	1.95E-03	0.93000	0.82000	1.04000
CigSmX	6 Cities	cardio	combined	20.3	3968.00	2.00E-01	1.05E-04	2.50E-05	1.85E-04	1.00002	1.00000	1.00004
CigSmC	6 Cities	cardio	combined	20.3	4960.00	2.00E-01	1.70E-04	8.99E-05	2.49E-04	1.00003	1.00002	1.00005

FROM ISI DOCUMENT SOLUTIONS (MON) 08. 13' 01 10:26/ST. 10:01/NO. 3560638488 P 17/21

PM3006519034

APPENDIX (cont.)

Agent	Author	End Point	Sex	Base ($\mu g/m^3$)	Exposure ($\mu g/m^3$)	Ambient ($\mu g/m^3$)	UR per $\mu g/m^3$ Beta	Beta LL	Beta UL	ACR/Ambient Conc. Risk	Risk LL	Risk UL
CigSmC	ACS	cardio	combined	0.0	4960.00	2.00E-01	1.65E-04	1.20E-04	2.15E-04	1.00003	1.00002	1.00004
PM_{10}	AHSMOG	NMRD	male	0.0	83.90	2.00E+01	8.70E-03	−2.56E-03	1.99E-02	1.19000	0.95000	1.49000
PM_{10}	AHSMOG	NMRD	female	0.0	83.90	2.00E+01	3.85E-03	−6.39E-03	1.39E-02	1.08000	0.88000	1.32000
CigSmX	AHSMOG	NMRD	male	41.9	4762.00	2.00E-01	5.00E-06	2.50E-06	5.00E-06	1.00000	1.00000	1.00000
CigSmX	AHSMOG	NMRD	female	41.9	3175.00	2.00E-01	5.00E-06	−5.00E-06	1.50E-05	1.00000	1.00000	1.00000
$PM_{2.5}$	citiesStub	lung	combined	11.0	29.60	2.00E+01	1.68E-02	−1.12E-02	4.50E-02	1.40000	0.80000	2.46000
CigSmX	8 Cities	lung	combined	11.0	3968.00	2.00E-01	2.34E-04	−2.50E-05	4.98E-04	1.00025	0.99999	1.00017
CigSmC	8 Cities	lung	combined	11.0	4960.00	2.00E-01	4.18E-04	2.20E-04	6.21E-04	1.00008	1.00004	1.00012
$PM_{2.5}$	ACS	lung	male	9.0	33.50	2.00E+01	4.77E-03	−8.72E-03	1.57E-02	1.10000	0.84000	1.37000
$PM_{2.5}$	ACS	lung	female	9.0	33.50	2.00E+01	−4.17E-03	−2.38E-02	1.50E-02	0.92000	0.62000	1.35000
$PM_{2.5}$	ACS	lung	combined	9.0	33.50	2.00E+01	0.90E-04	−9.32E-03	1.16E-02	1.02000	0.85000	1.26000
CigSmC	ACS	lung	combined	21.3	4960.00	2.00E-01	4.59E-04	3.59E-04	5.57E-04	1.00008	1.00007	1.00011
PM_{10}	AHSMOG	lung	male	9.0	83.90	2.00E+01	5.04E-02	1.86E-02	8.19E-02	2.74000	1.45000	5.15000
PM_{10}	AHSMOG	lung	female	9.0	83.90	2.00E+01	1.20E-02	−2.15E-02	4.50E-02	1.27000	0.65000	2.46000
CigSmX	AHSMOG	lung	male	41.9	4762.00	2.00E-01	1.40E-04	5.00E-05	2.05E-04	1.00003	1.00000	1.00004
CigSmX	AHSMOG	lung	female	41.9	3175.00	2.00E-01	2.15E-04	−1.50E-04	5.96E-04	1.00004	0.99997	1.00012
Diesel	Johnston	lung	male	0.0	10.00	1.00E+00	−1.82E-02	−2.45E-01	2.82E-01	0.98156	0.78239	1.32551
Diesel	Johnston	branch	male	0.0	10.00	1.00E+00	1.82E-02	9.55E-03	2.78E-02	1.0840	1.00380	1.02820
Diesel	Johnston	total	male	0.0	10.00	1.00E+00	−9.40E-03	−1.17E-02	−7.30E-03	0.99084	0.98837	0.99273
Diesel	Severin	lung	male	0.0	70.00	1.00E+00	7.40E-03	−1.02E-02	2.51E-02	1.00749	0.98985	1.02542
Diesel	Severin	cardio	male	0.0	70.00	1.00E+00	−1.90E-03	−1.74E-02	1.34E-02	0.99870	0.98275	1.01349
Diesel	Severin	total	male	0.0	70.00	1.00E+00	1.20E-03	−4.30E-03	6.70E-03	1.00120	0.99571	1.00672
Diesel	Severin	resp	male	0.0	43.00	1.00E+00	−6.72E-03	−1.66E-02	2.00E-03	0.9930	0.9836	1.00200
Diesel	Steenland	lung	male	0.0	1.25	1.00E+00	1.46E-01	−1.89E-01	4.75E-01	1.15709	0.82814	1.60747
Diesel	Steenland	lung	male	0.0	3.15	1.00E+00	4.71E-02	−8.30E-02	1.78E-01	1.04825	0.92038	1.19441
Diesel	Steenland	lung	male	0.0	4.45	1.00E+00	7.40E-02	−2.12E-02	1.66E-01	1.07681	0.979031	18269
Diesel	Steenland	lung	male	0.0	5.10	1.00E+00	1.06E-01	2.05E-02	1.90E-01	1.11220	1.02067	1.20987
Diesel	Steenland	lung	male	0.0	1.00log cum exposure by regression					1.00260	1.00050	1.00450
CarbnBlk	Robertson	circu	male	0.0	a	3.00E-01	−8.20E-03	−1.81E-02	1.80E-03	0.99754	0.99458	1.00054
CarbnBlk	Robertson	MI	male	0.0	b	3.00E-01	−8.10E-03	−1.71E-02	5.00E-03	0.99817	0.99488	1.00150
CarbnBlk	Robertson	resp	male	0.0	c	3.00E-01	0.00E+00	−4.67E-01	4.72E-01	1.00000	0.86935	1.15208
PAH	Costantino	lung	male	0.0	327.00	5.00E+00	7.17E-03	−5.42E-03	1.98E-02	1.03650	0.97328	1.10394
PAH	Costantino	lung	male	0.0	327.00	5.00E+00	2.96E-03	8.15E-04	5.47E-03	1.01499	1.00408	1.02770
PAH	Costantino	lung	male	0.0	327.00	5.00E+00	2.05E-03	1.20E-03	3.15E-03	1.01030	1.00603	1.01586
PAH	Costantino	lung	male	0.0	327.00	5.00E+00	1.39E-03	8.68E-04	2.30E-03	1.00699	1.00435	1.01155
PAH	Costantino	lung	male	0.0	327.00	5.00E+00	1.45E-03	9.99E-04	2.22E-03	1.00726	1.00501	1.01117
PAH	Costantino	lung	male	0.0	327.00	5.00E+00	1.14E-03	8.83E-04	1.52E-03	1.00572	1.00445	1.00762
PAH	Costantino	cardio	male	0.0	327.00	5.00E+00	1.00E-04	−2.00E-04	3.00E-04	1.00050	0.99900	1.00150
PAH	Costantino	arterio	male	0.0	327.00	5.00E+00	1.00E-04	−2.00E-04	4.00E-04	1.00050	0.99900	1.00200

FROM ISI DOCUMENT SOLUTIONS (MON) 08. 13' 01 10:26/ST. 10:01/NO. 3560638488 P 18/21

PM3006519035

Source: https://www.industrydocuments.ucsf.edu/docs/nngj0001

APPENDIX (cont.)

Agent	Author	End Point	Sex	Base ($\mu g/m^3$)	Exposure ($\mu g/m^3$)	Ambient ($\mu g/m^3$)	UR per $\mu g/m^3$ Beta	Beta LL	Beta UL	AER/Ambient Conc. Risk	Risk LL	Risk UL
PAH	Costantino	hyperlens	male	0.0	327.00	5.00E+00	1.00E-04	−8.00E-04	9.00E-04	1.00050	0.99501	1.00451
PAH	Costantino	NMRD	male	0.0	327.00	5.00E+00	5.00E-04	−2.00E-04	1.20E-03	1.00250	0.99900	1.00602
PAH	Costantino	total	male	0.0	327.00	5.00E+00	2.00E-04	1.00E-04	4.00E-04	1.00100	1.00050	1.00200
PAH	Armstrong	lung	male	7.2	70.00	5.00E+00	1.95E-03	−2.43E-03	6.46E-03	1.00978	0.98793	1.03282
PAH	Armstrong	lung	male	7.2	214.00	5.00E+00	3.92E-03	1.96E-03	5.89E-03	1.01980	1.00985	1.02968
PAH	Armstrong	lung	male	7.2	358.00	5.00E+00	1.83E-03	5.67E-04	3.10E-03	1.00919	1.00284	1.01564
PAH	Armstrong	lung	male	7.2	500.00	5.00E+00	1.49E-03	5.32E-04	2.44E-03	1.00746	1.00267	1.01229
PAH	Armstrong	lung	male	0.0	0.00log cum exposure by regression					1.00000	1.00000	1.00000
BaP	Armstrong	lung	male	0.7	0.79	2.00E-03	4.61E+00	1.01E+00	8.15E+00	1.00927	1.00203	1.01544
BaP	Armstrong	lung	male	0.7	2.15	2.00E-03	5.55E+01	2.62E-01	8.45E-01	1.00111	1.00052	1.00169
BaP	Armstrong	lung	male	0.7	3.57	2.00E-03	2.58E-01	1.17E-01	3.99E-01	1.00052	1.00023	1.00080
BaP	Armstrong	lung	male	0.7	5.00	2.00E-03	1.46E-01	1.13E-02	2.80E-01	1.00029	1.00002	1.00056
BaP	Armstrong	lung	male	0.0	0.00log cum exposure by regression					1.00000	1.00000	1.00000
SiO_2	Checkoway	lung	male	3.6	11.40	3.00E+00	−2.24E-02	−1.11E-01	5.80E-02	0.99514	0.97630	1.02641
SiO_2	Checkoway	lung	male	3.6	22.60	3.00E+00	−4.28E-02	−8.93E-02	3.03E-03	0.97961	0.78496	1.00915
SiO_2	Checkoway	lung	male	3.6	50.70	3.00E+00	−2.47E-03	−1.74E-02	1.25E-02	0.99260	0.94905	1.03615
SiO_2	Checkoway	lung	male	3.6	65.00	3.00E+00	6.00E-03	−2.29E-03	1.42E-02	1.01817	0.99316	1.04356
SiO_2	Checkoway	NMRD	male	3.6	11.40	3.00E+00	5.37E-02	−7.66E-02	1.84E-01	1.17473	0.79458	1.73665
SiO_2	Checkoway	NMRD	male	3.6	22.80	3.00E+00	3.56E-02	−1.50E-02	8.61E-02	1.11764	0.95604	1.29480
SiO_2	Checkoway	NMRD	male	3.6	50.70	3.00E+00	1.80E-02	−2.90E-03	3.80E-02	1.05554	0.99407	1.12088
SiO_2	Checkoway	NMRD	male	3.6	65.00	3.00E+00	1.92E-02	8.58E-03	3.04E-02	1.05949	1.02606	1.09557
SiO_2	Checkoway	total	male	3.6	22.80	3.00E+00	1.03E-03	−3.22E-03	4.49E-03	1.00310	0.99038	1.01956
SiO_2	Checkoway	ischas	male	3.6	22.80	3.00E+00	−1.03E-02	−1.78E-02	−2.67E-03	0.96947	0.94729	0.99202
SiO_2	Reid	lung	male	0.0	53.00	3.00E+00	7.93E-03	−2.13E-03	1.83E-02	1.02406	0.99363	1.05658
SiO_2	Reid	COPD	male	0.0	53.00	3.00E+00	1.27E-02	0.00E+00	2.35E-02	1.03809	1.00000	1.07314
SiO_2	Reid	ischae	male	0.0	53.00	3.00E+00	4.06E-03	2.84E-03	5.52E-03	1.01225	1.00794	1.01670
SiO_2	Reid	cerebro	male	0.0	53.00	3.00E+00	1.63E-03	−2.20E-03	5.09E-03	1.00489	0.99343	1.01540
SiO_2	Reid	total	male	0.0	53.00	3.00E+00	4.95E-03	4.06E-03	5.85E-03	1.01496	1.01225	1.01713
SiO_2	Holzdo	lung	male	19.3	50.80	3.00E+00	1.83E-02	−7.08E-03	4.48E-02	1.05645	0.97857	1.14383
SiO_2	Holzdo	lung	male	19.3	77.20	3.00E+00	9.40E-03	−1.20E-02	2.01E-02	1.01328	0.96472	1.05212
SiO_2	Holzdo	lung	male	19.3	110.00	3.00E+00	7.25E-03	−2.46E-03	1.77E-02	1.02199	0.99265	1.05488
SiO_2	Steenland	lung	male	0.0	2.30	3.00E+00	6.83E-02	−7.07E-02	1.96E-01	1.22726	0.80898	1.80103
SiO_2	Steenland	lung	male	0.0	11.45	3.00E+00	8.69E-04	−3.12E-02	3.00E-02	1.00261	0.91078	1.09420
SiO_2	Steenland	lung	male	0.0	22.95	3.00E+00	−1.33E-03	−3.78E-02	2.62E-02	0.99603	0.89279	1.08827
SiO_2	Steenland	lung	male	0.0	35.00	3.00E+00	7.72E-03				1.02342	
SiO_2	Steenland	pneumoc	male	0.0	2.30	3.00E+00	2.53E-01	3.35E-02	4.48E-01	2.13702	1.10560	3.83045
SiO_2	Steenland	pneumoc	male	0.0	11.45	3.00E+00	3.31E-02	−1.22E-02	7.31E-02	1.10424	0.96417	1.24529
SiO_2	Steenland	pneumoc	male	0.0	22.95	3.00E+00	4.71E-02	1.50E-02	7.38E-02	1.15190	1.04594	1.24723
SiO_2	Steenland	pneumoc	male	0.0	35.00	3.00E+00	6.24E-02	5.33E-02	7.07E-02	1.20573	1.17356	1.23631
SiO_2	Steenland	ISD	male	0.0	18.30	3.00E+00	−3.38E-03	−8.88E-03	1.62E-03	0.98991	0.97371	1.00486
SiO_2	Steenland	cerebro	male	0.0	18.30	3.00E+00	−3.38E-03	−1.57E-02	9.04E-03	0.98991	0.95393	1.02750

FROM ISI DOCUMENT SOLUTIONS (MON) 08. 13'01 10:27/ST. 10:01/NO. 3560638488 P 19/21

PM3006519036

Source: https://www.industrydocuments.ucsf.edu/docs/nngj0001

APPENDIX (cont.)

Agent	Author	End Point	Sex	Base ($\mu g/m^3$)	Exposure ($\mu g/m^3$)	Ambient ($\mu g/m^3$)	UR per $\mu g/m^3$ Beta	Beta LL	ACR/Ambient Conc. Beta UL	Risk	Risk LL	Risk UL
SiO_2	Steenland	total	male	0 0	18.30	3 00E+00	6,68E-03	3.70E-03	9.51E-03	1.02074	1 01115	1 02899
SiO_2	Ulm	lung	male	11 2	31.70	3.00E+00	−2 50E-03	−3,58E-02	2 07E-02	0 99252	0.89878	1 06421
SiO_2	Ulm	lung	male	11 2	54.00	3.00E+00	−1 95E-03	−1.92E-02	1,11E-02	0.99417	0.94403	1 03394
SiO_2	Ulm	lung	male	11 2	90.00	3 00E+00	4 98E-04	−8.06E-03	8.08E-03	1.00149	0.97612	1 02453
SiO_2	McLaughlin	lung-pol	male	0 0	62 50	3 00E+00	9 40E-03		1,02882			
SiO_2	McLaughlin	lung-pol	male	0 0	250 00	3 00E+00	1 62E-03		1.00488			
SiO_2	McLaughlin	lung-pol	male	0 0	450.00	3.00E+00	1 65E-03		1 00496			
SiO_2	McLaughlin	lung-tun	male	0,0	62.50	3 00E+00	5 38E-03		1,01628			
SiO_2	McLaughlin	lung-tun	male	0,0	250 00	3,00E+00	3 81E-04		1.00714			
SiO_2	McLaughlin	lung-tun	male	0 0	450 00	3,00E+00	−7,54E-05		0.99539			
SiO_2	McLaughlin	lung-lin	male	0 0	62.50	3.00E+00	4 20E-03		1.01267			
SiO_2	McLaughlin	lung-lin	male	0.0	250 00	3.00E+00	1 05E-03		1.00315			
SiO_2	McLaughlin	lung-un	male	0 0	450 00	3.00E+00	−7,93E-04		0,99762			
SiO_2	Cherry	lung	male	0 0	57 00	3 00E+00	9,95E-03	-1.63E-01	1.74E-01	1,03050	0.61413	1 68516
SiO_2	Cherry	heart	male	0 0	57 00	3 00E+00	−3 54E-04	−3 27E-03	2 14E-03	0,99894	0.99024	1.00645
SiO_2	Cherry	cerebro	male	0.0	57 00	3 00E+00	−3 91E-03	−1,36E-02	4.33E-03	0 98832	0.95995	1.01308
SiO_2	Cherry	total	male	0.0	57 00	3 00E+00	2 45E-03	8.56E-04	4 05E-03	1 00738	1.00257	1.01224
SiO_2	Cherry	NMRD	male	0 0	57.00	3.00E+00	1 25E-02	7.69E-03	1 71E-02	1 03824	1.02333	1.05269
As	Jarup	lung	male	0 0	1,80	9.50E-04	5.54E-01	2 18E-01	9.41E-01	1.00053	1.00021	1 00180
As	Jarup	lung	male	0 0	8 80	9 50E-04	1,46E-01	7 41E-02	2.06E-01	1.00014	1.00007	1.00020
As	Jarup	lung	male	0 0	27 90	9.50E-04	3 11E-02	1.18E-02	4.80E-02	1.00003	1 00001	1 00005
As	Jarup	lung	male	0 0	128.00	9.50E-04	9 51E-03	4,97E-03	1.34E-02	1 00001	1.00000	1.00001
As	Jarup	lung	male	0 0	464,80	9,50E-04	3 29E-03	2.43E-03	4 07E-03	1 00000	1.00000	1.00000
As	Jarup	lung	male	0 0	1072.50	9.50E-04	1 85E-03	9.16E-04	2.58E-03	1 00000	1 00000	1.00000
As	Jarup	lung	male	0 0	3000 00	9.50E-04	8,10E-04	5.91E-04	9.96E-04	1 00000	1.00000	1.00000
As	Jarup	ISD	male	0 0	1 80	9.50E-04	0,00E+00	−1 38E-01	1.33E-01	1 00000	0,99987	1.00013
As	Jarup	ISD	male	0 0	8 80	9.50E-04	1 59E-02	−1 71E-02	4 81E-02	1,00002	0.99998	1.00004
As	Jarup	ISD	male	0.0	27 90	9.50E-04	−7.24E-04	−8.45E-03	6 23E-03	1 00000	0.99999	1.00001
As	Jarup	ISD	male	0 0	128 00	9 50E-04	1 55E-04	−1 74E-03	1 99E-03	1 00000	1,00000	1,00002
As	Jarup	ISD	male	0 0	464 80	9.50E-04	2,63E-04	−1 56E-04	6 82E-04	1.00000	1 00000	1.00000
As	Jarup	ISD	male	0.0	1072,50	9 50E-04	4 21E-04	−6,77E-05	8 36E-04	1 00000	1 00000	1 00000
As	Jarup	ISD	male	0 0	3000 00	9 50E-04	3.78E-05	−1 29E-04	1 81E-04	1.00000	1,00000	1.00000
As	Jarup	cerebro	male	0,0	1,80	9,50E-04	4 28E-02	−2,39E-01	2.88E-01	1 00004	0.99977	1.00027
As	Jarup	cerebro	male	0 0	8,80	9 50E-04	5 41E-02	−3 46E-03	1,05E-01	1 00005	1.00000	1.00010
As	Jarup	cerebro	male	0 0	27 90	9 50E-04	−2,60E-03	−1 83E-02	1.15E-02	1.00000	0.99998	1.00001
As	Jarup	cerebro	male	0 0	128 00	9 50E-04	−2 68E-03	−7 16E-03	1,23E-03	1,00000	0 99999	1.00000
As	Jarup	cerebro	male	0 0	464,80	9,50E-04	4.28E-04	−9.24E-04	1,12E-03	1.00000	1,00000	1.00000
As	Jarup	cerebro	male	0 0	1072.50	9 50E-04	3.33E-04	−7 24E-04	1 12E-03	1.00000	1 00000	1.00000
As	Jarup	cerebro	male	0 0	3000.00	9 50E-04	−1.24E-04	−6.54E-04	1 92E-04	1.00000	1 00000	1 00000
As	Lee-Feldst	lung	male	0 0	5952 00	9 50E-04	4 50E-05	−2.20E-05	1.18E-04	1.00000	1 00000	1,00000
Cr	Simonato	lung	male	0 0	3 50	5 50E-04	5 91E-02	−1 98E-01	2 66E-01	1.00003	0 99989	1.00015

FROM ISI DOCUMENT SOLUTIONS
(MON) 08. 13' 01 10:27/ST. 10:01/NO. 3560638488 P 20/21
PM3006519037
Source: https://www.industrydocuments.ucsf.edu/docs/nngj0001

APPENDIX (cont.)

Agent	Author	End Point	Sex	Base ($\mu g/m^3$)	Exposure ($\mu g/m^3$)	Ambient ($\mu g/m^3$)	UR per $\mu g/m^3$ Beta	Beta LL	Beta UL	ACR/Ambient Conc. Risk	Risk LL	Risk UL
Cr	Simonato	lung	male	0.0	10.00	5.50E-04	5.31E-02	−7.26E-03	1.05E-01	1.00003	1.00000	1.00006
Cr	Simonato	circ	male	0.0	7.10	5.50E-04	−8.71E-03	−2.12E-02	−2.85E-03	1.00000	0.99999	1.00000
Cr	Simonato	resp	male	0.0	7.10	5.50E-04	−5.23E-02	−0.76E-02	−1.02E-02	0.99997	0.99995	0.99999
Cr	Simonato	total	male	0.0	7.10	5.50E-04	−1.02E-02	−1.96E-02	−2.85E-03	0.99999	0.99999	1.00000
Ni	Simonato	lung	male	0.0	3.50	3.80E-03	2.43E-01	2.84E-03	4.37E-01	1.00092	1.00001	1.00166
Ni	Simonato	lung	male	0.0	10.00	3.80E-03	1.22E-02	−1.17E-01	1.06E-01	1.00005	0.99956	1.00040
Ni	Simonato	circ	male	0.0	7.10	3.80E-03	−8.71E-03	−2.12E-02	−2.85E-03	0.99997	0.99992	0.99999
Ni	Simonato	resp	male	0.0	7.10	3.80E-03	−5.23E-02	−9.76E-02	−1.02E-02	0.99980	0.99963	0.99996
Ni	Simonato	total	male	0.0	7.10	3.80E-03	−1.02E-02	−1.96E-02	−2.85E-03	0.99996	0.99993	0.99999

Notes: [a]Exposure = difference between cases (192 $\mu g/m^3$) and controls (240 $\mu g/m^3$). UR = ln(1.61)/−48.0 = 0.99. [b]Exposure = difference between cases (192 $\mu g/m^3$) and controls (249.5 $\mu g/m^3$). UR = ln(1.42)/−57.5 = 0.99. [c]Exposure = difference between cases (192 $\mu g/m^3$) and controls (240 $\mu g/m^3$). UR = ln(1.00)/−1.6 = 1.00.

Agent: Cig Sm = cigarette smoke particulate (PM_1); CigSmC = current; CigSmX = former; Diesel = diesel particulate (PM_1)

Author: Cities = Six Cities PM cohort study;[2] citiesTope = Topeka; citiesW = Watertown; citiesSTL = St. Louis; citiesSteub=Steubenville; citiesHarr=Harriman. ACS = American Cancer Society PM cohort study.[3] AHSMOG = Adventist Health Study of Smog.[3,4]

Mortality End Point: Total = all-cause mortality; cardio = cardiopulmonary in PM cohort studies, lung = lung cancer, lung-occ is among pottery workers, lung-lun is among lungsam miners, and lung-irn is among iron-copper miners; NMRD = nonmalignant respiratory disease, circ = cardiovascular disease, bronch = bronchitis; MI = myocardial infarction; resp = respiratory; hypertens = hypertension; arterio = arteriosclerosis, ISD = ischemic heart disease; COPD = chronic obstructive pulmonary disease, cerebro = cerebrovascular disease; pneumoc = pneumoconiosis, such as silicosis

Base: Lifetime average exposure of referent group in $\mu g/m^3$

Exposure: Lifetime average exposure in $\mu g/m^3$, this is the midpoint of exposure categories in occupational studies

Ambient: Average concentration of agent in ambient air and used in calculation of ACR

Unit Risk (UR): Beta = coefficient of point estimate of UR/1-$\mu g/m^3$ PM, Beta LL = coefficient of lower 95% confidence interval of UR, Beta UL = coefficient of upper 95% confidence interval of UR

Ambient Concentration Risk (ACR): Risk = ACR per AMBIENT (beta × ambient) or point estimate of ACR; Risk LL = lower 95% confidence interval of ACR; Risk UL = upper 95% confidence interval of ACR

FROM ISI DOCUMENT SOLUTIONS (MON) 08. 13' 01 10:27/ST. 10:01/NO. 3560638488 P 21/21

PM3006519038

Source: https://www.industrydocuments.ucsf.edu/docs/nngj0001